Dynamic susceptibility contrast perfusion MRI (with pitfalls)

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Introduction

Since the first studies in the late 1980s and early 1990s, *dynamic susceptibility contrast MRI* (DSC-MRI, also known as '*bolus tracking*') has become a very powerful technique for the assessment of perfusion[1], and perfusion-related parameters (see (1,2) for recent reviews). Despite the need of an exogenous MR agent (cf. arterial spin labeling techniques), DSC-MRI is currently the most common MR perfusion methodology in clinical studies. It relies on the injection of a *bolus of a paramagnetic contrast agent* (usually gadolinium-DTPA), which produces a transient decrease in signal intensity on a series of *gradient-echo or spin-echo images* acquired during its passage through the brain (3). The loss in signal intensity is due to the decrease in T_2* (or T_2)[2] associated with the susceptibility-induced gradients surrounding the paramagnetic contrast agent (4). This effect is more significant in areas where the contrast agent is compartmentalized (since this increases the induced gradients) and makes quantification of cerebral perfusion in areas with blood-brain barrier (BBB) leakage more complex (see later).

Since the passage of the bolus through brain tissue is of the order of a few seconds, a *very fast imaging method is required* to fully characterize the induced signal changes. The most common imaging technique currently used is EPI (5), which allows for a good compromise between time resolution (typical TR≈1.5sec), image coverage (typically 10-15 slices) and spatial resolution (typical voxel size 2x2x5mm[3]). However, other image acquisitions can be used if full brain coverage is required (e.g. 3D-PRESTO (6)), or if improved spatial resolution is necessary (e.g. segmented EPI).

Quantification – Indicator dilution theory

The changes in relaxation rate (ΔR_2*) are related to the concentration of the contrast agent: the larger the concentration, the larger the observed effect. Early work has suggested that this *relationship* can be *assumed to be linear* (3,4,7):[3]

$$C(t) = k \cdot \Delta R_2^*(t) \tag{1}$$

where *C(t)* is the time dependent contrast concentration, and *k* is a proportionality constant that depends on the tissue type, the contrast agent, the field strength, and the pulse sequence. Therefore, if *one assumes negligible T1 effects* during the bolus passage, *C(t)* can be calculated from the changes in signal intensity with respect to its baseline (i.e. pre-injection) value:

$$C(t) = -\frac{k}{TE} \cdot Ln\left(\frac{S(t)}{S_0}\right) \tag{2}$$

where *S(t)* is the signal intensity at time *t*, S_0 is its baseline value, and *TE* the echo-time of the MR sequence.

The concentration in the tissue is not only proportional to CBF, but it is also affected by how the study is done (for example, a slower injection will lead to a wider *C(t)*). Using indicator dilution theory, the concentration time course can be shown to be expressed by a *convolution* equation (12,13):

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[1] Throughout this document the terms *perfusion*, *cerebral blood flow* (and its acronym *CBF*) will be used indistinguishable.

[2] For the remainder of this document, all the statements referring to T_2* are also applicable to T_2.

[3] Although a linear relationship is usually used, recent studies have suggested that this *linear relationship may not always be valid*, particularly for large contrast concentration such as in big vessels (8,9). Therefore, although the assumption of a linear relationship may be valid for the concentration in the tissue, it may be a significant source of error in the measurement of the arterial input function (see later). Possible solution: use the phase information of the MR images (9-11).

$$C(t) = \alpha \cdot CBF\big(C_a(t) \otimes R(t)\big) = \alpha \cdot CBF \int_0^t C_a(\tau)R(t-\tau)d\tau \qquad (3)$$

where the symbol $\otimes$ indicates the convolution operation, $C_a(t)$ is the _arterial input function_ (AIF), i.e. the function describing the contrast agent input to the tissue of interest, and $R(t-\tau)$ is the tissue _residue function_, which describes the fraction of contrast agent remaining in the tissue at time t, following the injection of an ideal instantaneous bolus at time τ.[4] The proportionality constant α depends on the density of brain tissue, and the difference in hematocrit levels between capillaries and large vessels (to compensate for the fact that only the plasma volume is accessible to the contrast agent) (1). The integral in Eq.(3), accounts for the fact that for a non-ideal bolus, part of the spread in the concentration time curve is due to the finite length of the actual bolus. It is possible to interpret the integral expression in Eq.(3) by considering the AIF as a superposition of consecutive ideal boluses "$C_a(\tau)d\tau$" injected at time τ. For each ideal bolus, based on the definition of the residue function, the concentration still present in the tissue at time t will be proportional to "$C_a(\tau)R(t-\tau)d\tau$", and the total concentration $C_t(t)$ will be given by the sum (or integral) of all these contributions.

Quantification – Deconvolution

Quantification of CBF therefore involves inversion of Eq.(3), a mathematical process known as _deconvolution_ (13). This _requires measurement of the AIF_, and calculating the scaled residue function $CBF \cdot R(t)$ (known as the impulse response function). Once this function is calculated, perfusion can be obtained from its initial value, since $R(t=0)=1$ by definition.[5]

Although inverting Eq.(3) (i.e. performing the deconvolution) may appear simple at first sight, this inverse problem is known mathematically as an _ill-posed problem_. This means that even a tiny amount of noise in the measured concentration curves will have huge effect on the calculated impulse response (and thus CBF!). To deal with this issue, a special approach (known as _regularization_) is required to make the inversion problem more stable to the presence of noise.[6] Therefore, a considerable amount of work has been done in the last decade to develop, assess, and compare various deconvolution algorithms; a lot of this work involved the use of numerical simulations, where the conditions can be modified in a controlled way, and the actual answer is known. Some of the algorithm proposed to date include: Fourier Transform approach (13,14), singular value decomposition (SVD) and its variants (13,15-17), maximum-likelihood maximization (18), Tikhonov regularization (19), expansion in orthogonal polynomials (20), and Gaussian processes deconvolution (21). Ideally an algorithm should lead to accurate measurements under a wide a range of practical situations, such as under various tissue characteristics (e.g. perfusion values, residue function models), imaging characteristics (e.g. SNR levels), sequence parameters (e.g. TR, TE), as well as for other experimental conditions (such as the presence of bolus delay to areas with abnormal vascular supply). Furthermore, the algorithm should be fast to be able to be used in a clinical environment. Unfortunately, there is currently no single algorithm that fulfils all these requirements; the likely reason for the lack of consensus between users. It is for this reason that this is still an area of very active research.

Quantification – Other physiological and hemodynamic parameters

DSC-MRI can provide information not only about perfusion but also about other physiological and hemodynamic parameters. For example, due to the compartmentalization of the contrast agent within the intravascular space (for an intact BBB)[7], the _cerebral blood volume_ (_CBV_) is proportional to the normalized total amount of tracer (1):

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[4] By definition, $R(0)=1$, i.e. no tracer has left the tissue at time $t=\tau$ after an ideal instantaneous bolus injected at time τ, and $R(\infty)=0$, i.e. at very long times, no tracer remains in the tissue if the BBB is intact and the contrast is washed out by perfusion.
[5] Although in theory the initial value of the impulse response determines perfusion, in many cases the maximum value of the function is used instead (13). The presence of bolus dispersion (see later) distorts the shape of the calculated impulse response function such that $R(0)=0$.
[6] The regularization can be seen as a 'filter' applied during the inversion problem, which aims at reducing the effect of noise while recovering the true impulse response function. Many regularization methods have been developed, depending on the characteristics of the 'filter'. For any regularization method, a key (and usually complex) aspect is to determine the right amount of filtering once the 'filter' type is chosen.
[7] When the BBB is not intact, quantification of CBV is more complicated; the calculation must account for the contrast agent in the extravascular space (see later).

$$CBV = \alpha^{-1} \frac{\int C_t(t)dt}{\int C_a(t)dt} \qquad (4)$$

where the proportionality factor α^{-1} is the inverse of the factor in Eq.(3). The normalization to the integral of AIF accounts for the fact that, the more tracer is injected the greater concentration will reach the tissue, regardless of the CBV. A third physiological parameter accessible by DSC-MRI is the *mean transit time* (*MTT*: the average time for a molecule of contrast agent to pass through the tissue vasculature following an ideal instantaneous bolus injection). These three physiological parameters are not independent, but they are related through the *central volume theorem* (22): MTT=CBV/CBF.

Other *hemodynamic parameters* (also known as *summary parameters*) can also be calculated directly from the profile of the *C(t)* curve as *indirect* perfusion measures (1). There are several different parameters, such as bolus arrival time (BAT), time to peak (TTP), i.e. time until the maximum of *C(t)*, maximum peak concentration (MPC), i.e. maximum value of *C(t)*, and full-width at half maximum (FWHM). It should be noted that most of these parameters can be influenced not only by CBF, but also by CBV, MTT, the injection conditions (volume injected, injection rate, cannula size, etc), the vascular structure, and the cardiac output of the patient. Therefore, the interpretation of abnormalities observed in these parameters in terms of perfusion is not straightforward (23,24). Nevertheless, they are simpler to calculate (they do not require deconvolution or knowledge of the AIF) and can provide useful information; for example, the BAT identifies areas for which the bolus is delayed, which can provide information regarding the presence of collateral blood supply.

Quantification – Absolute units

DSC-MRI can provide, in principle, CBF in *absolute units* (typically ml/100g/min). There are three main approaches to achieve this:
1. *Use of an internal standard*: since CBF measurements using PET have initially suggested a relatively age-independent and uniform white matter value of 22 ml/100g/min in normal adults, a region in normal white matter was proposed as an internal standard to convert the MR measurement to absolute units (25).
2. *Knowledge of the proportionality constants*: if the values of the constants appearing in the equations above are known, the deconvolution method would lead to absolute measurements (14,20,26-28).
3. *Use of a scaling factor obtained from a cross-calibration study*: the MR CBF values can be converted to absolute units by using an empirical conversion factor calculated (usually from a separate study) by cross-calibration of DSC-MRI to a 'gold standard' technique (e.g. PET) (29,30).

Although all these approaches have been used to calculate perfusion in absolute units and the values obtained in normal subjects are consistent with expected CBF values, *there are still some concerns* regarding the accuracy under various physiological conditions (31-34), and the agreement might have been fortuitous. In principle, all the approaches can potentially lead to errors, particularly in the presence of pathology. For example, a recent study has shown a wide variability in white matter CBF values measured with PET on the contralateral hemisphere in patients with chronic carotid occlusion (35). Similarly, some studies have shown that the constant k in Eq.(1) may vary between tissue types, subjects, as well as between tissue and arteries (8,36). Furthermore, changes in hematocrit levels (and therefore α) during pathology have been reported (37,38). Similarly, the validity of a single conversion factor under various physiological conditions remains to be shown (34,35,39). Therefore, absolute CBF measurements in the presence of pathology should be interpreted with caution. Work is currently under way to address many of these issues, and accurate absolute measurements of CBF may be possible in the near future.

Measurement of the AIF

One of the first questions that arise when using the deconvolution approach is '*Where should one measure the AIF?*'. As a 'general rule':
   a) one should measure the AIF in a voxel with pure intravascular signal (for a true reflection of the arterial signal);
   b) one should measure it as close as possible to the tissue of interest (for a proper characterization of the input to that tissue).

The main problem is that these conditions are incompatible: while *(a)* requires measuring the AIF from voxels in a large artery such as the internal carotid artery (to avoid partial volume effects (40)), *(b)* requires measuring it from the small arterial branch supplying the particular tissue of interest (41). Therefore, if one favors *(a)*, the AIF measurement will be subject to the potential presence of bolus *delay and dispersion* between the artery and the tissue of interest; which can introduce errors in CBF quantification (41-43).[8] On the other hand, if option *(b)* is favored, significant *partial volume effects* are likely to distort the shape of the true AIF, potentially also introducing CBF errors (9,34,40,44). Given these limitations, the most commonly used approach to measuring the AIF is a compromise between these two conditions: the AIF is generally measured from a major branch of the middle cerebral artery (usually the M1 segment). It is generally acknowledged that *inaccuracy in the AIF measurement is one of the major potential sources of error* in perfusion quantification. Therefore, it is important to recognize that errors related to partial volume effects and bolus dispersion can be present when interpreting the calculated DSC-MRI maps.

Global vs. Local AIF

As mentioned in the previous section, the AIF is commonly measured in a major artery, and this estimated function used as a *global AIF* for the whole dataset. To minimize the errors related to bolus dispersion, it has been proposed that a *local AIF* should be used instead (45-46).[9] This approach is likely to be particularly sensitive to partial volume effects, and various methods to define a local AIF have been proposed. Although further work is required to validate these approaches, they may prove to be a promising solution to *minimizing the dispersion-related errors* in certain group of patients, such as those with arterial stenosis or occlusion.

Quantification – BBB breakdown

The kinetic model described in Eq.(3) is based on the assumption that the contrast agent remains intravascular. If this not the case (e.g. when the *BBB is disrupted*), the distribution of the contrast agent outside the vascular compartment *decreases the T2* effects*, as well as *increases the T1 effects* (usually neglected) during the passage of the bolus. If these effects are not minimized (47) or taken into account (48), significant errors can be introduced in quantification of DSC-MRI data (see (49) for a recent review). Although the use of a dual echo sequence (to calculate T_2^*) has been shown to eliminate the confounding effects of T_1 enhancement (48), this is done at the expense of reducing the maximum number of slices available. In order to account for the T_1 effects, Weisskoff et al (50) *modeled the MR signal in terms of the combined T1 and T2* contributions*. In such a way, they proposed a method to quantify CBV in the presence of contrast leakage, as well as an estimation of vascular permeability (50,51). More recently, this work has been extended to quantify not only CBV and a measure of permeability, but also CBF (48,52). Since the effects of contrast leakage are included, it should provide a more accurate estimation of perfusion when the BBB is disrupted, although a full validation of these modified models remains to be done.

Conclusion

DSC-MRI is a very powerful technique that provides unique information regarding cerebral hemodynamics. It has been extensively used for the assessment and management of patients, as well as being an invaluable tool in experimental studies. The principles of measuring perfusion using DSC-MRI have been reviewed. The main assumptions and steps required for CBF quantification were described. The main limitations and artifacts that can affect the accuracy of CBF quantification were discussed. Solutions to many of these limitations are the subject of current research. In the interim, these issues should be taken into consideration whenever DSC-MRI is used to

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[8] Although some of the deconvolution algorithms are prone to errors due to bolus delay (e.g. (13)), there are now many algorithms which have been shown to be *delay-insensitive* (e.g. (14,16-18)). Their use is highly advisable, especially in patients with vascular abnormalities where bolus delay are likely to occur (32). The *errors due to bolus dispersion* are not related to the particular deconvolution algorithm used, but they are a *more fundamental limitation of the model* used in Eq.(3); this equation assumes that the *true* AIF is measured, and the unaccounted dispersion will be then assigned to occurring within the tissue of interest (i.e. interpreted as a prolonged MTT and decreased CBF (32)). Therefore, it should be noted that while the particular choice of deconvolution algorithm can remove the delay-related errors, it cannot eliminate those associated to bolus dispersion.

[9] In fact, by definition the AIF should be calculated on a pixel-by-pixel basis because the input to the tissue can be potentially different for each voxel (depending on its blood supply).

measure perfusion, and the users of these techniques should be aware of the potential problems to avoid misinterpretation of the findings, and make the most of the invaluable information provided by perfusion MRI.

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